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### III. REMARKS

Reconsideration of the application, as amended, is respectfully requested.

The undersigned gratefully acknowledges the courtesies extended by Examiners Gollamudi and Hartley during the interview conducted on June 27, 2003. During the interview all of the pending claims were discussed. Also during the interview, Alberts et al. (U.S. Patent No. 4,997,658), Cheng et al. (Pharmaceutical Research article), Oshlack et al. (U.S. Patent No. 5,472,712) and Sako et al. (U.S. Patent No. 6,436,441) were discussed.

#### A. Pending Claims

Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and new independent claims 76-81 are pending. Claims 14-17, 20, 23-24, 30, 55-56, 72-75 are cancelled without prejudice by virtue of this amendment.

#### B. Rejections Under 35 U.S.C. § 112

During the interview, the rejection of the claims on the grounds of non-enablement was discussed. The Examples of the present application provide formulations, methods of making the formulations and clinical studies of these formulations that support the limitations (e.g.,  $T_{max}$  values) recited in the present claims. The undersigned explained that the specification in no uncertain terms states that other controlled release technologies beyond that exemplified can be used, and provides sufficient guidance to one skilled in the art to manufacture such alternative formulations without undue experimentation. This statement is found at page 19, line 36 through page 20, line 6 of the specification. It was further pointed out during the interview that the specification *then, at length, continues* to explain how other types of controlled release formulations could be prepared (from page 20, line 7 through page 24, line 14). The information included therein pertains to multiparticulate systems (such as (i) coated beads, (ii) spheroids, (iii)

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matrix particles; all of which may be coated as set forth on pages 21-22). Alternatively, normal and controlled release matrix formulations are described on pages 22-24.

It was further pointed out during the interview that the claimed invention is directed in part to formulations and methods which functionally provide certain characteristics in-vivo (and in-vitro, in certain claims). It was submitted that one of ordinary skill in the art *having the information provided in the present specification* would be able to manufacture formulations other than those specifically exemplified in the Examples, which formulations would perform in accordance with the claimed invention. It was pointed out that the fact that the state of the art is such that one of ordinary skill could achieve these goals if provided with the information contained in the present application is acknowledged by the Examiner, who alludes to the fact that "Alberts discloses that this controlled release can be achieved by a variety of procedures known to those skilled in the art. The procedures suitable for the invention are diffusion-controlled systems, osmotic devices, dissolution controlled matrices, and erodible/degradable matrices (col. 3, lines 1-2)." (Office Action dated April 4, 2003, Paper No. 15, page 6). It was further noted that the Cheng reference relied upon by the Examiner discusses testing of sustained release matrix tablets (referred to therein as SRT8 and SRT14), and so such technologies were clearly available to one of ordinary skill in the art as of the filing date of the present application.

The case law is respectfully submitted to support applicants' position on enablement. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); MPEP 2164.01 (8<sup>th</sup> Edition). "Nothing more than objective enablement is required, and therefore, it is irrelevant whether [a] teaching is provided broad terminology or illustrative examples." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In addition, the case law does not require each possible formulation

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encompassed by the claims to be exemplified. See e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 84 (CCPA 1970); MPEP 2164.01(b) (8<sup>th</sup> Edition) (see previous response).

It was explained during the interview that once having arrived at the inventive concept (e.g., the  $T_{max}$  range), reduced it to practice, and demonstrated it to be useful as in the present invention, one skilled in the art having the information contained in the specification would without undue experimentation be able to manufacture formulations falling within the claims via a myriad of controlled release technologies such as those discussed in detail in the specification.

In view of the arguments presented during the interview (and herein), it is respectfully submitted that the specification supports an uncoated formulation with the same in-vivo parameters, and that coatings are not "critical".

Claims 14, 23-23, 30, 55-56 and 58 were rejected under 35 U.S.C. 112, second paragraph, the Examiner stating that the instant claims depend upon a parent claim that recites a given range and the instant claims are not within the range of the parent claim.

As discussed during the interview, claims 30 and 56 indeed were inadvertently directed to a  $T_{max}$  of the drug which is outside of the claimed range of the independent claim. These claims have now been cancelled. Furthermore, during the interview it was pointed out that the remaining claims were either directed to the  $T_{max}$  of an active metabolite (lovastatin acid), or were directed to the  $T_{max}$  of total HMG-CoA Reductase Inhibitors (e.g., lovastatin plus active metabolites), rather than solely the drug contained in the formulation itself (e.g., lovastatin). Therefore, these claims were not actually referring to the same  $T_{max}$  as the independent claim. However, in order to clarify the claims and to avoid misinterpretation, the claims directed to the  $T_{max}$  of lovastatin acid or total HMG-CoA Reductase Inhibitors have now been cancelled without prejudice to pursuing such claims in a continuation application. Thus, claims 14, 15-17, 20, 23-24 and 55-56 have been cancelled. On the other hand, claim 58 was rejected by the Examiner on

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the same basis. However, claim 58 is an *independent claim* directed to a  $T_{max}$  at about 10.4 to about 20.6 hours after oral administration of a single dose of lovastatin. This claim has a  $T_{max}$  range that is *narrower* than claim 1, in any event, and is directed to the results of Study 1, Table 6, page 45 of the specification.

It is respectfully submitted that all of the issues raised by the Examiner under 35 USC 112 second paragraph have now been addressed and have been overcome. It is respectfully requested that this rejection now be removed in its entirety.

C. Rejections Under 35 U.S.C. § 103

In the Office Action, the Examiner rejected claims 1-75 under 35 U.S.C. 103(a) as being unpatentable over Alberts et al. (U.S. Patent No. 4,997,658) or Cheng et al. (Pharmaceutical Research) in view of Oshlack et al. The Examiner also rejected claims 1-75 under 35 U.S.C. 103(a) as being unpatentable over Alberts et al. (U.S. Patent No. 4,997,658) or Cheng et al. (Pharmaceutical Research) in view of Sako et al. (U.S. Patent No. 6,436,441).

As discussed during the interview, there are different ways to prepare a solid dosage form of a drug to obtain a prolonged effect when administered to, e.g., human patients. Alberts et al. concerns a method of administering an HMG-CoA Reductase Inhibitor utilizing a drug-delivery device for the controlled release of the drug into an environment of use. (See, column 2, lines 55-58). The expression "time-controlled administration" as used in Alberts et al. is deemed to encompass the release of the active form or pro-drug form of the HMG-CoA Reductase Inhibitor into the environment of use over a period of 6 to 24 hrs. The only information in Alberts et al. directed to the in-vivo performance of its formulations is found at Example 2, columns 5-6. In that example, a HMG-CoA Reductase Inhibitor (the ring opened dihydroxy acid of simvastatin) was administered to dogs as either an oral bolus dose or as an oral controlled release preparation. The controlled-release preparation afforded controlled in-vitro release of the drug over a 6-10

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hour period. (See, column 5, lines 63-66). Table 2 provides serum cholesterol and plasma drug levels for this example. There is no information contained in this example as to the desired time to maximum plasma concentration after oral administration of the drug ( $T_{max}$ ). In addition, the peak circulating plasma drug level (which is believed to represent a  $C_{max}$ ) is very different than the peak level set forth in the present claims.

As discussed during the interview, the Cheng reference (which describes work supported by the assignee of the Alberts patent) describes studies conducted with seven sustained/controlled-release dosage forms of lovastatin or simvastatin. The *in-vivo* performance of these formulations was evaluated in dogs and healthy volunteers. The results are reported Table II on page 1685 and Table V page 1687 of the Cheng reference. (As pointed out by the undersigned, page 1686 of this reference was not included in the copy of this reference provided to applicants).

In Table V, the controlled-release formulations are reported to have a  $T_{max}$   $4.2 \pm 0.7$  hours (MODS8) and  $4.7 \pm 1.0$  hours (MODS14, representing the  $T_{max}$  for an 8 hour formulation and a 14 hour formulation, respectively. It is apparent from this data that these formulations have been designed to provide a relatively rapid rise in plasma concentration to  $T_{max}$ , and it is respectfully submitted that the results are not suggestive of a mean  $T_{max}$  as set forth in the present claims (which occurs at a time which is more than double the time for the  $T_{max}$  of the 14 hour Cheng formulation). It is noted that the  $T_{max}$  reported in Table V is the  $T_{max}$  for total HMG-CoA Reductase Inhibitors in healthy subjects receiving a single dose of 20 mg simvastatin.

Turning now to Table II of the Cheng reference, this table provides pharmacokinetic parameters of total HMG-CoA Reductase Inhibitors *in dogs* receiving a single oral dose of 80 mg lovastatin. The  $T_{max}$  reported therein for the sustained and controlled-release formulations are as follows: SRT8 had a  $T_{max}$  of  $1.8 \pm 0.4$ ; SRT14 had a  $T_{max}$  of  $2.3 \pm 0.8$ ; CRS8 had a  $T_{max}$  of  $4.0 \pm 0.0$ ; and CRS14 had a  $T_{max}$  of  $7.5 \pm 1.2$ . However, as discussed during the interview, it was

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respectfully submitted that all of that data concerning dog values is not instructive with respect to the performance of these formulations in humans given that the Cheng reference at page 1687, left column, penultimate paragraph states the following: "By comparing the AUC and  $C_{max}$  ratios for CRS and MODS formulations in dogs (Tables II and III) to those in humans (Table V), it can be concluded that the dog may not be a good model for predicting relative bioavailability of lovastatin or simvastatin in these formulations in humans)." (Emphasis added).

During the interview, the undersigned noted that the Examiner and the undersigned were missing a page of the Cheng reference. Therefore, submitted herewith as Exhibit A is a complete copy of the Cheng reference for the Examiner's review and consideration. The undersigned has reviewed the complete copy of the Cheng reference and notes that the complete copy does not alter the arguments discussed herein.

As discussed during the interview, the Oshlack '712 patent is directed to stabilized solid controlled-release formulations having a coating derived from an aqueous dispersion of a hydrophobic polymer obtained by curing the coated substrate under specified conditions to stabilize the release profile. The only data provided in this patent directed to in-vivo results is data directed to opioid analgesics, which is not in any way related to, e.g., HMG-CoA Reductase Inhibitors. In any event, as discussed during the interview, one of the results reported had a  $T_{max}$  greater than 7.8 hours (See, Table 52, column 40 of the '712 patent). With respect to the Examiner's assertion that Figure 16 of Oshlack teaches a  $T_{max}$  of 9, it is respectfully submitted that the Examiner's position is not correct. One can not determine a  $T_{max}$  from a plasma concentration curve as the  $T_{max}$  is taken from the time that the maximum concentration is reached whenever that occurs during the dosing interval, whereas, the Examiner is reading the mean concentration at the 9 hour time point on the plasma concentration curve depicted in Figure 16 (which is a different number).

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During the interview, Examiner Hartley asked the undersigned if the  $T_{max}$  was dependent upon the time that the dosage forms of the invention were administered. The undersigned pointed out at that time that while there may be some variation of  $T_{max}$  depending upon the time that the drug is administered, the  $T_{max}$  is always greater than about 10 hours as can be seen from the  $T_{max}$  values for the Lovastatin XL exemplified and tested formulations as set forth in Tables 6, page 45 of the specification of the present application. It was further pointed out to the Examiner for this very reason, the claims as written were not necessary reflective of the  $T_{max}$  obtained in a single study.

**D. New Claims**

In this amendment, new claims 76-81 have been added. These claims set forth the  $T_{max}$  range (including standard deviation) for study number 5 (40 mg dose), study number 4 (bedtime/single dose), and study number 1 with (dinner/single dose). Support for these claims are found throughout the specification, and in particular in Table 6, page 45 of the specification.

Finally, the Sako et al. reference is directed to hydrogel-type sustained-release preparations which may be used for a wide variety of drugs. None of the exemplified formulations includes a drug that is a HMG-CoA Reductase Inhibitor, and no information is provided in this reference concerning generalized or desired time to maximum plasma concentration for any drug, let alone a HMG-CoA Reductase Inhibitor.

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IV. Conclusion


It is now believed that the above-referenced rejections have been obviated and withdrawal is respectfully requested. It is believed that all claims are now in condition for allowance.

An early and favorable action is earnestly solicited.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By:

  
Clifford M. Davidson  
Reg. No. 32,728

Davidson, Davidson & Kappel, LLC  
485 Seventh Avenue, 14th Floor  
New York, New York 10018  
(212) 736-1940